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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,932	07/18/2003	Subhashis Banerjee	BBI-8187RCE	3572

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,932	BANERJEE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-14 and 18-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-14 and 18-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7, 9 and 15-17 are cancelled.
Claims 8, 10, 13 and 18-25 have been amended.
Claims 27-43 have been added.

2. Claims 8, 10-14 and 18-43 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the specification as disclosing various non-provisional US Application numbers whose status has changed and require updating is withdrawn in view of the amendments to the specification filed 11/3/2008.

6. The objection to the title of the invention as not descriptive or clearly indicative of the invention to which the claims are directed is withdrawn in view of the newly submitted title filed 11/3/2008.

Objections/Rejections Maintained and New Grounds of Rejections

7. The provisional rejection of claims 8, 10-14, 18-26 and now applied to newly added claims 28-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, 16-21, 78-79, 81, 84, 86-88, 95, 97-98 and 100-104 of copending Application No. 10/163,657 in view of Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000) is maintained.

The response filed 11/3/2008 states that the rejection is provisional in nature and will be addressed when appropriate, i.e., when the nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the later-filed application.

Applicants' remarks are acknowledged, however, in view that the claims are rejected on other grounds and not presently in condition for allowance, the rejection is maintained.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/163,657, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

8. The provisional rejection of claims 8, 10-14, 18-25 and now applied to newly added claims 28-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 9-22, 25-26 and 28-53 of copending Application No. 11/104,117 in view of Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000) is maintained.

The response filed 11/3/2008 states that the rejection is provisional in nature and will be addressed when appropriate, i.e., when the nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the later-filed application. Applicants' remarks are acknowledged, however, in view that the claims are rejected on other grounds and not presently in condition for allowance, the rejection is maintained.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common

ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/104,117, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The rejection of claims 8, 10-14, 18-26 and now applied to newly added claims 28-43 under 35 U.S.C. 103(a) as being unpatentable over Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000, cited on PTO-892 mailed 9/6/06) in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, cited on PTO-892 mailed 9/6/06) and Keystone et al ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)", *Presented at the Annual Meeting of the Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic*, 2001, IDS reference C62 filed 5/28/08) is maintained.

The response filed 11/3/2008 argues the individual teachings of Oh et al, Salfeld et al [a] and Keystone et al, stating that Oh et al doesn't teach or suggest that a human anti-TNFα antibody could be used in a biweekly, subcutaneous dosing regimen involving the administration of the antibody in a unit dosage form that is independent of body weight and Salfeld et al [a] doesn't teach a dosage comprising 10-150 mg of a human anti-TNFα antibody, or antigen-binding fragment thereof, wherein the same dosage amount is administered throughout the course of treatment in accordance with the amended claims and Keystone et al is limited to the treatment of rheumatoid arthritis that is clinically and mechanistically different from psoriasis. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Additionally, the test for obviousness is not whether the features of a secondary reference may be bodily

incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant also states that the average clinician presented with a report describing the clinical efficacy of a particular dosing regimen for the treatment of one disease, *rheumatoid arthritis*, would understand that these results simply cannot be directly extrapolated to the treatment of a different disease, *psoriasis*, with a reasonable expectation of success. Applicant presents different dosing regimens for the chimeric TNFα antibiody, infliximab, used for treatment of psoriasis, rheumatoid arthritis and ankylosing spondylitis to support the position that the same agent to treat more than one disorder does not necessarily have the same dosing regimen. Applicant concludes that one of average skill in the art could not have reasonably predicted that a biweekly, subcutaneous dosage regimen of a human TNFα antibody, e.g., D2E7, to patients also receiving methotrexate as described by Keystone et al for treating rheumatoid arthritis would be successful in treating psoriasis based on Oh et al's observation that the psoriasis of a single patient demonstrated an improvement after two injections of infliximab as a supplement to a full spectrum of medications for psoriasis and Crohn's disease. Applicants' arguments have been fully considered but are not found persuasive. While Keystone et al do teach the subcutaneous biweekly administration of the fully human anti-TNFα antibody D2E7 as taught by Salfeld et al [a] at 20 mg, 40 mg and 80 mg for the treatment of *rheumatoid arthritis*, the teachings of Keystone et al indicate that the administered D2E7 antibody was well tolerated and therapeutically effective, particularly at 40 mg every other week. Thus, while one of ordinary skill in the art would recognize that the optimal dosing regimen for the D2E7 antibody may vary for the treatment of other TNFα-mediated disorders, such as psoriasis as taught by Oh et al, given the success of D2E7 administered subcutaneously at 20 mg, 40 mg and 80 mg every other week (i.e., biweekly), one of ordinary skill in the art would have been motivated to at least administer the D2E7 antibody or antigen-binding fragments thereof

subcutaneously at 20 mg, 40 mg or 80 mg every other week for the treatment of psoriasis. "[A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1397. Additionally, one of ordinary skill in the art would have been motivated to administer the fully human D2E7 antibody or antigen-binding fragments thereof subcutaneously at 20 mg, 40 mg or 80 mg every other week for the treatment of psoriasis in view of the limited and short-term efficacy of infliximab as taught by Oh et al. Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). In the instant case, one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Oh et al providing evidence that the administration of an anti-TNFα antibody is a clinically effective treatment for psoriasis.

With respect to newly added claims 28-43, it would have been *prima facie* obvious to administer the fully human D2E7 antibody or antigen-binding fragments thereof subcutaneously at 20 mg, 40 mg or 80 mg every other week for the treatment of psoriasis in patients regardless of the presence or absence of any prior treatment for psoriasis.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. The rejection of claims 18, 10-14, 18-26 and now applied to newly added claims 28-43 under 35 U.S.C. 103(a) as being unpatentable over Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000, cited on PTO-892 mailed 9/6/06) in view of Salfeld et al [b] (US Patent 6,509,015 B1, 2/9/1996, cited on PTO-892 mailed 9/6/06) and Keystone et al ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients

with Active RA on Methotrexate Therapy (The ARMADA Trial)", *Presented at the Annual Meeting of the Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* 2001, IDS reference C62 filed 5/28/08) is maintained.

The response filed 11/3/2008 argues as above and the examiner's remarks above apply here as well and are incorporated herein by reference. It is noted that the instant rejection differs only in the use of Salfeld et al [b], however, Salfeld et al [a] and [b] are equivalent teachings.

Therefore, as discussed supra the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. The rejection of claims 8, 10-14, 18-25 and now applied to newly added claims 28-43 on the ground of nonstatutory obviousness-type double patenting as being

unpatentable over claims 1-7, 36-39 and 69-70 of U.S. Patent No. 6,509,015 B1 in view of Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000, cited on PTO-8892 mailed 9/6/06) and Keystone et al ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)", *Presented at the Annual Meeting of the Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* 2001, IDS reference C62 filed 5/28/08) is maintained.

The response filed 11/3/2008 argues as above, i.e., the combined teachings of Salfeld et al, Oh et al and Keystone et al fail to provide a reasonable expectation of success for the treatment of psoriasis with biweekly, subcutaneous dosage regimen of human anti-TNFα antibody as presently claimed. Applicants' arguments have been fully considered but are not found persuasive for the reasons set forth above and incorporated herein by reference, and in view that no terminal disclaimer has been filed.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,509,015 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

14. The provisional rejection of claims 8, 10-14, 18-26 and now applied to newly added claims 28-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 11/233,252 (***allowed, not yet issued***) in view of Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000, cited on PTO-892 mailed 9/6/06) and Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, cited on PTO-892 mailed 9/6/06) and Keystone et al ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)", *Presented at the Annual Meeting of the Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* 2001, IDS reference C62 filed 5/28/08) is maintained.

The response filed 11/3/2008 argues as above, i.e., the combined teachings of Salfeld et al, Oh et al and Keystone et al fail to provide a reasonable expectation of success for the treatment of psoriasis with biweekly, subcutaneous dosage regimen of human anti-TNFα antibody as presently claimed. Applicants' arguments have been fully considered but are not found persuasive for the reasons set forth above and incorporated herein by reference, and in view that no terminal disclaimer has been filed.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/233,252, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

15. Claims 8, 10, 12 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oh et al (Journal of the American Academy of Dermatology, 42(5):829-830, 2000, cited on PTO-892 mailed 9/6/06) in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997, cited on PTO-892 mailed 9/6/06) and Keystone et al ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)", *Presented at the Annual Meeting of the Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* 2001, IDS reference C62 filed 5/28/08) and Neuner et al (Photochem Photobiol., 59(2):182-188, Feb 1994).

The claims are drawn to a method of treating psoriasis in a subject comprising biweekly, subcutaneous administration of a unit dosage form comprising 10-150 mg, 20-80 mg or about 40 mg of an anti-TNFα antibody or antigen-binding fragment thereof such that psoriasis is treated, wherein the anti-TNFα antibody or antigen-binding fragment thereof dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, or comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 or the antibody is D2E7, and is administered with one additional therapeutic agent, which is PUVA therapy.

Oh et al teach a method of treating psoriasis in a patient comprising administering a therapeutically effective amount of a humanized anti-TNFα monoclonal antibody (Infliximab). Oh et al do not specifically teach biweekly, subcutaneous administration of a unit dosage form comprising 10-150 mg, 20-80 mg or about 40 mg of an anti-TNFα antibody or antigen-binding fragment thereof such that psoriasis is treated, wherein the anti-TNFα antibody or antigen-binding fragment thereof dissociates

from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, or comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 or the antibody is D2E7, or administration with PUVA therapy. These deficiencies are made up for in the teachings of Salfeld et al [a] and Keystone et al and Neuner et al.

Salfeld et al [a] teach that because humanized antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [a] teach a method for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of the neutralizing, high affinity fully human D2E7 anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and is administered with one or more additional therapeutic agents (see entire document, particularly pp. 2-4, 5-6, 12-15, 29-31 and 35-40). Salfeld also teaches a variety of administration regimens, routes of administration, antibody fragments, antibody heavy chain constant regions, and dosages, such as 0.1-20 mg/kg (see entire document, in particular pp. 33-34). Salfeld also teaches that "[d]osage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation... It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person

administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition (see pp. 33-34). Thus, according to the teaching of Salfeld, *the dosage regimen for anti-TNFα antibody, including dosage scheduling and amount, is a recognized results-effective variable,* i.e., a variable that is recognized as important for therapeutic use of an anti-TNFα antibody and which therefore can be optimized by routine experimentation. See M.P.E.P. § 2144.05 II.B. and *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

Keystone et al teach that the fully human anti-TNFα antibody D2E7 administered subcutaneously at 20 mg, 40 mg and 80 mg every other week (i.e., biweekly) was well tolerated and therapeutically effective, particularly at 40 mg every other week (see entire document).

Neuner et al teach that psoralen plus UV-A (PUVA) is an effective therapy for psoriasis and inhibits TNFα production (see entire document).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the neutralizing, high affinity human D2E7 anti-human TNFα antibody or antigen-binding fragments thereof of Salfeld et al [a], and administered subcutaneously every other week at 20 mg, 40 mg or 80 mg (particularly 40 mg) with PUVA therapy for the treatment of psoriasis in a patient as taught by Oh et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to use the neutralizing, high affinity human D2E7 anti-human TNFα antibody or antigen-binding fragments thereof of Salfeld et al [a], and administered subcutaneously every other week at 20 mg, 40 mg or 80 mg (particularly 40 mg) with PUVA therapy for the treatment of psoriasis in a patient in view of Oh et al and Keystone et al and Neuner et al because Oh et al teach a method of treating psoriasis in a patient comprising administering a therapeutically effective amount of a humanized anti-TNFα monoclonal antibody (Infliximab), however, Salfeld et al [a] teach that because humanized

antibodies still retain some of murine sequence, they still may elicit an unwanted immune reaction in human patients and Salfeld et al [a] teach the neutralizing, high affinity fully human D2E7 anti-human TNFα antibody and antigen-binding fragments thereof for treating TNFα-related disorders in a subject comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., identical structures/sequences, binding kinetics and neutralization properties (discussed supra) and administered with one or more additional therapeutic agents and Keystone et al teach that the fully human anti-TNFα antibody D2E7 administered subcutaneously at 20 mg, 40 mg and 80 mg every other week (i.e., biweekly) was well tolerated and therapeutically effective, particularly at 40 mg every other week and Neuner et al teach that psoralen plus UV-A (PUVA) is an effective therapy for psoriasis and inhibits TNFα production. Therefore, one of ordinary skill in the art would have been motivated to modify the method of Oh et al and administer the fully human D2E7 anti-human TNFα antibody and antigen-binding fragments thereof subcutaneously at 20 mg, 40 mg or 80 mg every other week and in combination with PUVA therapy in order to avoid any unwanted immune reaction in human patients due to the presence of murine sequences in the humanized anti-TNFα antibody of Oh et al and subcutaneous administration at 20 mg, 40 mg or 80 mg every other week is well tolerated and therapeutically effective according to Keystone et al and PUVA therapy is an effective therapy for psoriasis and inhibits TNFα production according to Neuner et al. Thus, there are several advantages that would have led the ordinary skilled artisan to make the above modifications. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Oh et al providing evidence that the administration of an anti-

TNFα antibody is a clinically effective treatment for psoriasis and Neuner et al providing evidence that PUVA therapy is an effective therapy for psoriasis. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to produce a method of treating psoriasis in a human patient comprising biweekly, subcutaneous administration of the neutralizing, high affinity human D2E7 anti-human TNFα antibody or antigen-binding fragments thereof at 20 mg, 40 mg or 80 mg and administered with PUVA therapy in view of the teachings of Oh et al and Salfeld et al [a] and Keystone et al and Neuner et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00

AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643